Remarks

Claims 2-4 are pending.

By the above amendment, claim 2 has been rewritten to explicitly correlate the presence of the p10Ii fragment analyzed in step (d), which feature was previously recited in original claim 4, to the monitored effect of *in vivo* administration of the cathepsin S inhibitor recited in the preamble. Support for this amendment may be found in the specification, e.g., at page 6, last two sentences. The amendment is necessary and was not earlier presented because it is responsive to the Examiner's new ground for rejecting claim 2 for indefiniteness. Since the amendment introduces no new matter, reduces the issues for appeal, and places the claims in condition for allowance or better condition for appeal, its entry is respectfully requested.

In the final Office Action, the Examiner rejected claims 2-4 under 35 U.S.C. § 112, second paragraph, for indefiniteness. More particularly, the Examiner argued that claim 2 as previously presented was vague and indefinite in lacking a correlation of the presence of the p10Ii fragment analyzed in step (d) to the monitored effect of *in vivo* administration of the cathepsin S inhibitor recited in the preamble. As noted above, claim 2 has been amended to expressly recite the correlation. Accordingly, Applicants request withdrawal of the rejection under Section 112, paragraph two.

In the final Office Action, the previous rejection of claims 2-4 under 35 U.S.C. § 103(a), as being unpatentable over Chapman et al. (WO 99/58153) in view of Willmann et al. (US 6,495,333), was maintained. As indicated by the Examiner in the first Office Action, the Chapman et al. reference discloses a method for monitoring the effect *in vivo*

of a cathepsin S inhibitor by detecting the presence of invariant chain Ii on the surface of a cell. According to the Examiner, Example III of the primary reference discloses the evaluation of the effects of cathepsin S inhibitors on Ii degradation by obtaining a cell sample of splenocytes, lysing the cells, and then analyzing the lysates for the accumulation of an approximately 10 kDa fragment of Ii (i.e., pI0Ii). The Examiner noted that the claimed method differs from the Chapman et al. method in employing a blood sample. The Examiner applied the Willmann et al. reference as supposedly suggesting the detection of fragment p10Ii as taught by Chapman et al. using peripheral blood samples as taught by Willmann et al., because the secondary reference recognizes the difficulty in studying function in dendritic cells on account of their rarity but shows ease in collecting blood as opposed to lymphatic tissue, and achieves the goal of non-invasive procedures in monitoring compound activity for pharmaceutical evaluation studies of autoimmune disorders such as in the method of Chapman et al.

For the reasons explained in Applicants' response to the first Office Action, which for the sake of brevity are incorporated by reference herein, this rejection is in error. In reply to Applicants' arguments, the Examiner noted in the final Office Action that the claims employ open transitional terminology (i.e., "comprising"). That the claims literally read on methods employing steps in addition to those recited, however, does not cure the deficiencies of the rejection.

Attempting to shore up the rejection, the Examiner further argued that "one cannot show nonobviousness by attacking references individually where the rejections are based on [a combination] of references." The burden is not on Applicant to show

nonobviousness, however, but on the Examiner to show *prima facie* obviousness. Moreover, Applicants' previous arguments did not address solely the teachings of the individual references, but clearly pointed out why one of ordinary skill in the art would not have been motivated to combine the teachings of the individual references so as to arrive at the presently claimed invention.

Without hindsight knowledge of the present invention, the artisan would have lacked motivation to modify the Chapman et al. compound evaluation or diagnostic methods to analyze whole cell lysates of purified white blood cells from a blood sample for the presence of the p10Ii fragment as in the claimed invention. The Willmann et al. reference discloses a flow cytometric method for measuring dendritic cell function in whole blood, not a method for monitoring the effect *in vivo* of a cathepsin S inhibitor administered to a subject, let alone of detecting a p10Ii fragment. Since the methods of the two references are for distinct types of assays, the artisan would not have been motivated to combine their teachings.

Furthermore, even assuming *arguendo* that the artisan were to have looked to the secondary reference, there would have been no motivation to select and combine various aspects of its teachings with those of the primary reference so as to arrive at the claimed method. A determination of obviousness cannot be based on the hindsight combination of features selectively culled from the prior art to fit the parameters of the patented invention. ATD Corp. v. Lydall, Inc., 159 F.3d 534, 48 U.S.P.Q.2d 1321 (Fed. Cir. 1998).

Since the Examiner has not set forth a proper *prima facie* case of obviousness, the Section 103 rejection is in error and should be withdrawn.

In view of the foregoing, Applicants request prompt and favorable action. Additionally, Applicants again request the Examiner to initial the Forms PTO-1449 submitted with the Information Disclosure Statements dated November 26, 2001, and January 21, 2004, and return the initialed forms with the next official correspondence to confirm consideration of the cited references.

Respectfully submitted,

Date: March 21, 2005

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